

Efficacy and Safety of COX-2 Inhibitor Parecoxib for Rigid Cystoscopy-related Pain Management in Male Patients: A Prospective, Randomized and Controlled Study

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Summary: Using anesthetic gel may not sufficiently exclude pain perception during and after cystoscopy in male patients. To evaluate the analgesic efficacy and safety of intramuscular parecoxib (40 mg) for outpatient-based rigid cystoscopy, we performed a prospective, randomized and controlled study. Consecutive male patients requiring diagnostic cystoscopy in our hospital were divided into group A (1% tetracaine gel, $n=50$) and group B (parecoxib, $n=51$) at random. Patients received intramuscular injections of either 2 mL sterile saline in group A or 40 mg parecoxib in group B 30 min before the procedure. Tetracaine gel was injected into the urethra 3 min before the procedure in group A, with patients receiving plain lubricant gel in group B at the same time. Cystoscopy-associated pain levels were evaluated using the Visual Analog Score (VAS) during the procedure. Post-procedure urethral pain and complications were recorded and analyzed. The results showed that male patients experienced significantly less pain in group B than in group A (2.70 ± 1.36 vs. 3.56 ± 1.74 , $P=0.008$). The percentage of patients with dysuria pain was not significantly different between the two groups. In addition, 24 h after cystoscopy, the patients with no previous experience of cystoscopy were more likely to declare urethral pain (59.2% vs. 33.3%, $P=0.012$, relative risk=1.78). No difference was observed in analgesic-related complications between the two groups. We conclude that intramuscular injection of 40 mg parecoxib may improve comfort for male patients undergoing rigid cystoscopy.

Key words: cystoscopy; parecoxib; tetracaine gel; analgesia

Cystoscopy is a useful but painful procedure performed in the outpatient urology clinic^[1]. It is the principal means for diagnosis of bladder cancer. Due to high recurrence rates of bladder urothelial carcinoma, patients require post-surgery follow-up with repeated cystoscopy^[2]. However, patients may reject cystoscopy because of the pain associated with the procedure. In addition, patients complain of pain during urination that persists for several days following cystoscopy. Therefore, reduction of pain associated with this procedure has been desirable. Although a less painful, flexible cystoscope has been developed for clinical practice, rigid cystoscopies are still widely

used because they are more cost-effective and easier to maintain^[3].

Intraurethral topical anesthesia gel applied before the operation is widely used to address pain associated with cystoscopy. Nevertheless, the analgesic efficacy of topical anesthesia in cystoscopy is controversial. Some studies indicated that anesthesia gel with short dwell time is not significantly better than plain lubricant^[4, 5]. Moreover, male patients often complain of great pain during urination after cystoscopy due to their anatomical features. Therefore, more effective methods are needed to prevent or reduce cystoscopy-induced pain.

Cyclooxygenase (COX) enzymes mediate inflammatory prostaglandin production, which may be involved in nociception induced by cystoscopy. Oral analgesia by non-steroidal anti-inflammatory drug (NSAIDs) can control cystoscopy-associated pain through blocking COX signaling pathway^[6]. However,

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conventional NSAIDs nonspecifically inhibit both COX-1 and COX-2 enzymes, thus their uses can be limited due to the potential adverse effects of COX-1 inhibition, such as bleeding and gastrointestinal ulceration^[7]. The parenteral NSAID parecoxib is a selective COX-2 inhibitor, which avoids adverse effects caused by platelet inhibition^[8, 9]. In this prospective controlled study, we evaluated the analgesic effects and safety of intramuscular injection of parecoxib for rigid cystoscopy.

1 MATERIALS AND METHODS

1.1 Patients Enrollment

This study was approved by the Ethics Committee of Tongji Medical College (No. 2015s123). From May to September 2015, 122 consecutive male patients (>18 years old) who underwent outpatient rigid cystoscopy were recruited for this prospective controlled observational study. All patients were required to sign an informed consent to participate in the study. Exclusion criteria included: (1) urinary tract infection; (2) chronic pelvic pain; and (3) upper gastrointestinal hemorrhage.

1.2 Grouping and Procedures

Cystoscopy was carried out at the outpatient clinic of the Department of Urology, Union Hospital, Wuhan, China. Two experienced urologists performed all cystoscopies using a rigid F21 cystoscope (30° lens). A nurse recorded patient information, including history of cystoscopy and result of this cystoscopy.

Procedure duration time was monitored. An 11-point (0 to 10) Visual Analog Score (VAS) for pain (0: no pain, 10: worst possible pain) was evaluated by doctors and patients during the procedure. Postoperative urethral pain was monitored at 12 h and 24 h after operation by phone call, as well as hematuria, dizziness, pruritus, nausea and other adverse reactions.

We hypothesized that intramuscular parecoxib would be superior to standard topical urethral anesthesia with respect to pain perception during cystoscopy and urination after operation. We also assumed that during the procedure, VAS would be at least 30% lower in the parecoxib group. A mean VAS of 3.0 in the control group had been reported in a previous study^[10], so a sample size of 50 male patients in each group in our study was planned to detect a 30% difference in VAS and obtain 80% power using a one-side α value of 0.05.

1.3 Statistical Analysis

Results were analyzed by SPSS 20 (SPSS, Inc., USA) and outcomes were compared by using independent *t*-test and chi-squared test. Rank-sum test was used to compare paired continuous data. Parametric outcomes were expressed as the mean \pm standard deviation (SD). *P* values <0.05 were considered statistically significant.

2 RESULTS

A total of 122 consecutive male patients were assessed for eligibility. Sixteen patients did not meet inclusion criteria and 5 patients who declined to participate were excluded. Fifty-one patients were randomly assigned to group A and 50 to group B. Patients received intramuscular injections of either 2 mL sterile saline in group A or 40 mg parecoxib in group B 30 min before the procedure. Plain lubricant gel or tetracaine gel was injected into the urethra 3 min before the procedure in group B or group A. Patient characteristics are shown in table 1. No significant differences in age, weight, operating time or baseline pain duration were noted between the two groups.

Table 1 Characteristics of patients in the two groups

Parameters	Group A	Group B	<i>P</i> value
Number of patients	50	51	
Mean age (years)	55.7	51.6	>0.05
Mean weight (kg)	68.2	66.5	>0.05
Mean operating time (min)	6.4	6.8	>0.05
History of cystoscopy (<i>n</i> ,%)	12, 24%	24, 49%	0.01
Positive results (<i>n</i> , %)	27, 54%	17, 35%	>0.05
Baseline pain (VAS)	0.09	0.17	>0.05

As shown in table 2, the mean VASs assessed by patients in groups A and B were 3.56 \pm 1.74 and 2.70 \pm 1.36, respectively, with the difference being significant between the two groups (*P*=0.008). The mean VASs assessed by doctors in groups A and B were 1.71 \pm 0.71 and 1.63 \pm 0.639, respectively, with no statistically significant difference between the two groups (*P*=0.620). Meanwhile, the pain perception was significantly influenced by the cystoscopy results. The VAS for pain during cystoscopy was 3.65 \pm 1.88 for patients who were informed of the visualization of tumor or suspicion of tumor recurrence, and that was 2.70 \pm 1.27 in patients with negative cystoscopy results (patients' assessment, *P*=0.005).

The patients were followed up at 12 h and 24 h after cystoscopy. Statistically significant difference regarding urethral pain perception was noted depending on the history of cystoscopy in the past with no relation to the type of anesthesia used or the results of cystoscopy obtained (data not shown). As shown in table 3, 24 h after procedure, the percentage of patients experiencing urethral pain (including persistence pain and pain during urination) was significantly lower in patients with a history of cystoscopy (33.3% vs. 59.2%, *P*=0.012). We did not observe the differences in analgesic-related side effects such as dizziness, pruritus or nausea between the two groups (data not shown).

Table 2 Pain perception during cystoscopy assessed by using VAS

Parameters	VAS (mean±standard deviation)	
	Patient assessment	Doctor assessment
Groups		
A	3.56±1.74	1.71±0.74
B	2.70±1.36	1.63±0.89
<i>t</i> -value	2.722	0.498
<i>P</i> value	0.008	0.620
History of cystoscopy in the past		
No	3.28±1.8	1.83±0.81
Yes	3.00±1.71	1.47±0.73
<i>t</i> value	0.802	0.922
<i>P</i> value	0.522	0.060
Results of current cystoscopy		
Negative	2.70±1.27	1.69±0.92
Positive	3.65±1.88	1.67±0.71
<i>t</i> value	2.899	0.060
<i>P</i> value	0.005	0.911

Table 3 The percentage of patients with post-operation urethra pain at different time points

Time points (h)	Urethral pain	History of cystoscopy (<i>n</i> and percentage)		<i>P</i> value
		No	Yes	
0	No	0 (0%)	0 (0%)	
	Yes	49 (100%)	45 (100%)	
12	No	7 (14.3%)	12 (26.7%)	0.135
	Yes	42 (85.7%)	33 (73.3%)	
24	No	20 (40.8%)	30 (66.7%)	0.012
	Yes	29 (59.2%)	15 (33.3%)	

3 DISCUSSION

Cystoscopy equipment has been significantly improved in recent years and clinical application of the flexible cystoscope can relieve the discomfort and pain of cystoscopy^[11]. Pretreatment of the male urethra with topical anesthetic remains the top choice of most physicians for pain management. In the present study, we showed that intramuscular parecoxib was superior to tetracaine gel in lowering discomfort during cystoscopy. Meanwhile, there was a trend of decrease in the percentage of patients with painful urination following the procedure, although no statistical significance was found. In addition, we found that urethral pain following the cystoscopy was highly correlated with the history of cystoscopy in the past, which is in accordance with previous studies^[10, 12].

COX plays an important role in nociception induced by physical invasion. NSAIDs profoundly affect COX-related pain perception. Komiya *et al* conducted a prospective comparative study of analgesic effects of NSAIDs vs. lidocaine gel, and found preemptive NSAIDs decreased pain associated with cystoscopy^[6]. Intramuscular NSAIDs offer the most effective sustained analgesia for urologic pain and widely used in clinical practice^[13]. However, the

use of NSAIDs was limited by adverse effects such as gastrointestinal ulceration and enhanced risk of bleeding^[14]. Parecoxib, a selective COX-2 inhibitor, we found, provided a notable analgesic effect without prolonging hematuria after cystoscopy. We also did not observe gastrointestinal effects caused by parecoxib. Parecoxib effectively and safely improved the tolerability during the procedure.

Topical anesthetic agents directly interact with voltage-gated Na⁺ channels, reversibly blocking action potentials and nerve conduction^[15]. Urologists attributed greater male pain from cystoscopy to a longer urethra. It is plausible that use of topical anesthetic agents or doubling dosage would enhance efficacy. Previous studies failed to show significantly greater pain relief from the use of high volume topical anesthetic agent in aged men^[5]. Pliskin *et al* found no additive effect of topical anesthetic agents in cystoscopy^[16]. Moreover, a double-blind randomized study comparing pain relief between intraurethral anesthetic agent and plain lubricant showed that topical anesthetic agents might not provide satisfactory analgesic effects for rigid cystoscopy^[4]. Urethral irritation thus may not be the primary or major cause of high intensity pain during cystoscopy in men.

In male patients the most painful step during

rigid cystoscopy is insertion of the cystoscope into the urethra^[17]. The flexible cystoscope is softer and thinner, and most discomfort associated with use of a flexible cystoscope occurs during the injection of anesthetic gel. Reduced stimulus to the posterior urethra from a flexible cystoscope would explain decreased pain perception in male patients^[18]. Cystoscopy-related pain in men may in fact arise from the level of prostate and external sphincter. Dilation of the prostatic urethra and external sphincter by the cystoscope results in high intensity pain in men. This pain cannot be relieved by topical anesthetic agents, which anesthetize the mucosa. With no prostate and tight sphincter, female patients are unlikely to experience severe pain during cystoscopy.

The pain perception during cystoscopy was influenced by the result of the current cystoscopy^[19]. In this study, patients who were informed of a tumor or suspicion of tumor recurrence during the cystoscopy had higher VAS values than those with negative results found (3.65 ± 1.88 vs. 2.70 ± 1.27 , $P=0.005$). This may be explained by the fact that suspicious tumors needed to be particularly visualized, which consequently increased the amount of cystoscope manipulation. In addition, we found that the history of cystoscopy in the past positively influenced post-operation urethral pain, which is in accordance with previous study^[12]. Men, who undergo cystoscopy for first time, were more likely to experience urethral pain at 24 h after operation. Hence, we should provide enough analgesia for patients, especially for those who had a positive result in the current procedure or had a history of cystoscopy before.

Both parecoxib and tetracaine gel could decrease pain perception during cystoscopy, targeting different signaling pathways. It is possible that the combined use of parecoxib and topical analgesia would further alleviate discomfort. The limiting number of the subjects precluded such an analysis in the current study. Habituation effect may decrease VAS in patients with prior experience of cystoscopy, but in the current study, patients with or without a history of cystoscopy before reported similar VAS (as shown in table 2). The percentage of patients with prior experience of cystoscopy in group A was significantly lower than that in group B (table 1), which may affect the results in our study. Studies have reported that double volumes of analgesic gel (30 mL) or longer interval (20 min) between application of topical anesthetic and cystoscope insertion yielded improved pain tolerability^[20, 21]. However, application of double volumes of analgesic gel may over-expand the urethra, which would increase suffering during anesthesia. Further, analgesic gel was administrated after disinfection, thus longer interval increased procedure time by 15–20 min in a busy outpatient setting and raised patient anxiety by

prolonged maintenance of a lithotomy position.

In this study, preemptive parecoxib significantly decreased pain experienced during cystoscopy. Administration of parecoxib did not increase side effects, such as gastrointestinal hemorrhage. Parecoxib is a safe and efficacious analgesic, and can be recommended for use before rigid cystoscopy.

Conflict of Interest Statement

The authors declare that there is no conflict of interest with any financial organization or corporation or individual that can inappropriately influence this work.

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